RLY 04031.101
2004-003.A101.US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Dominique Charmot et al. Art Unit: 1618
Serial No.: 10/814,749
Filed: March 30, 2004
Confirmation No.: 7226
For: ION BINDING COMPOSITIONS
Examiner: Micah Paul Young

March 18, 2010

APPEAL BRIEF

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This is an appeal from the final rejection of the claims of the above-referenced application made in the Office action dated September 18, 2009. A Notice of Appeal was filed on December 18, 2009.

I. REAL PARTY IN INTEREST

The real party in interest in connection with the present appeal is Relypsa, Inc., the assignee of record.

II. RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any pending appeals or interferences which may be related to, directly affect or be affected by, or have a bearing on, the Board's decision in the present appeal.

III. STATUS OF CLAIMS

Claims 3, 4, 15, 21, 29, 30, 34, 40, 51-64 and 66-76 are pending. Claims 1-2, 5-14, 16-20, 22-28, 31-33, 35-39, 41-50, and 65 are canceled. A copy of the pending claims appears in the Claims Appendix of this Brief.

Claims 3, 4, 15, 21, 29, 30, 34, and 51-59, 62-64, 66-73, and 76 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Notenbomer (EP 0 730 494) in view of Cohen et al. (U.S. Patent No. 6,558,665). Claims 3, 34, 40, and 53 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Notenbomer (EP 0 730 494) in view of Cohen et al. (U.S. Patent No. 6,558,665) and Chong et al. (U.S. Patent No. 4,389,590). Claims 3, 53, 60, 61, 74, and 75 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Notenbomer (EP 0 730 494) in view of Cohen et al. (U.S. Patent No. 6,558,665), Shimizu et al. (U.S. Patent No. 5,824,339) and Macek et al. (U.S. Patent No. 3,499,960).

Applicants appeal the rejections of claims 3, 4, 15, 21, 29, 30, 34, 40, 51-64 and 66-76 under U.S.C. § 103(a) as being unpatentable.

IV. STATUS OF AMENDMENTS

No amendments were made after the final Office action. The pending claims are set out in the Claims Appendix.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter is generally directed to a pharmaceutical composition comprising core-shell particles.

Independent claim 3 is directed to an oral or rectal[1] pharmaceutical composition comprising core-shell particles and a pharmaceutically acceptable excipient. The core-shell particles comprise a core component and a shell component[2] wherein the core component comprises a potassium-binding cation exchange polymer[3] and the shell component comprises a crosslinked polymer having a thickness ranging from about 0.002 microns to about 50 microns.[4] The shell component is also essentially not disintegrated during residence and passage through the gastro-intestinal tract of an animal subject.[5]

Independent claim 34 is directed to a method of treating an animal subject suffering from a disease selected from the group consisting of renal insufficiency, renal failure, end stage renal disease (ESRD) and combinations thereof and comprises administering an effective amount of the pharmaceutical composition of claim 3 or 53 to an animal subject in need thereof.[6]

Independent claim 40 is directed to a method of treating an animal subject suffering from hyperkalemia and comprises administering an effective amount of the pharmaceutical composition of claim 3 or 53 to an animal subject in need thereof.[7]

Independent claim 53 is directed to an oral or rectal[1] pharmaceutical composition comprising core-shell particles and a pharmaceutically acceptable excipient. The core-shell particles comprises a core component and a shell component[2] wherein the core component comprises a potassium-binding cation exchange polymer[3] and the shell component comprises a crosslinked polymer. The weight ratio of the shell component polymer to the core component polymer ranges from about 0.0001:1 to about 0.5:1[8] and the shell component is essentially not disintegrated during residence and passage through the gastro-intestinal tract of an animal subject.[5]

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[1] *See* specification at paragraph [0076].
[2] *See* specification at paragraph [0008].
[3] *See* specification at paragraph [0019].
[4] *See* specification at paragraph [0046].
[5] *See* specification at paragraph [0014].
[6] *See* specification, original claims 38 and 40.
[7] *See* specification, original claims 39 and 40.
[8] *See* specification at paragraph [0047].

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Appellants appeal the rejection of claims 3, 4, 15, 21, 29, 30, 34, and 51-59, 62-64, 66-73, and 76 under 35 U.S.C. § 103(a) as being unpatentable over Notenbomer (EP 0 730 494) in view of Cohen et al. (U.S. Patent No. 6,558,665). Appellants further appeal the rejection of claims 3, 34, 40, and 53 under 35 U.S.C. § 103(a) as being unpatentable over Notenbomer (EP 0 730 494) in view of Cohen et al. (U.S. Patent No. 6,558,665) and Chong et al. (U.S. Patent No. 4,389,590). Also, Appellants appeal the rejection of claims 3, 53, 60, 61, 74, and 75 under 35 U.S.C. § 103(a) as being unpatentable over Notenbomer (EP 0 730 494) in view of Cohen et al. (U.S. Patent No. 6,558,665), Shimizu et al. (U.S. Patent No. 5,824,339) and Macek et al. (U.S. Patent No. 3,499,960).

VII. ARGUMENT

A. 35 U.S.C. § 103 Rejection over Notenbomer in view of Cohen

Claims 3, 4, 15, 21, 29, 30, 34, 51-59, 62-64, 66-73, and 76 are patentable over Notenbomer (EP 0 730 494) in view of Cohen et al. (U.S. Patent No. 6,558,665) under 35 U.S.C. § 103(a).

Claims 3 and 53

Reconsideration is respectfully requested of the rejection of claims 3, 4, 15, 21, 29, 30, 34, 51-59, 62-64, 66-73, and 76 as unpatentable over Notenbomer (EP 0 730 494) in view of Cohen et al. (U.S. Patent No. 6,558,665) under 35 U.S.C. § 103(a). Independent claims 3 and 53 are summarized above. The main reference, Notenbomer appears similar by generally disclosing methods and particles for binding monovalent cations. The Notenbomer particles have a nucleus and a coating; the nucleus contains a cation exchange material and the coating comprises a membrane that is permeable for monovalent cations. This coating is disclosed as being more permeable for monovalent cations than for bi- or higher valent cations. Exemplified cation exchange materials are polyphosphate and polystyrene sulfonate resins. Exemplified coatings are cellulose acetate and crosslinked polyethyleneimine. Generally, these particles are disclosed for treating hypertension. Notenbomer does not disclose the thickness of the shells or the shell to core weight ratio as required by claims 3 and 53, respectively. Thus, Notenbomer does not

describe all the elements of claims 3 or 53 because it does not describe the required thickness or the required shell to core weight ratio.

Cohen et al. describes methods of coating particles with a coating of uniform thickness that conforms to the size and shape of the particles. In particular, the particles coated are islet cells that are used to treat diabetes. The particles can be coated with poly(ethylene glycol) or poly(oxyethylene)-poly(oxypropylene) block copolymers or agarose that have a thickness of from about 10 microns to about 20 microns.[9]

The Office states that it "would have been obvious to coat the particles to a uniform thickness of 10-20 microns as disclosed in the '665 patent" and a skilled person "would have been motivated to combine the teachings [disclosure] and suggestions of the prior art as such with an expected result of a stable coated cation exchange resin useful in removing cations from the intestinal tract of a human."[10]

Applicants submit that the above rejection is in error for the following reasons.

As is well known, the determination of whether a claim is obvious within § 103(a), depends on at least four underlying factual issues set forth in *Graham v. John Deere Co. of Kansas City*[11]: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) evaluation of any relevant secondary considerations. In April 2007, the Supreme Court affirmed the *Graham* analysis as the framework for determining obviousness.[12]

In addressing the scope and content of the prior art, references are not pertinent to an obviousness inquiry if they are not from analogous art.[13] A reference is analogous art if: (1) the reference is from the same field of endeavor, regardless of the problem addressed, or (2) the reference is not within the inventor's field of endeavor, yet it is reasonably pertinent to the particular problem addressed by the inventor.

In *Clay*, the PTO asserted that the claimed invention and the Sydansk reference were analogous art because they were part of a common endeavor of "maximizing withdrawal of petroleum stored in petroleum reservoirs."[14] Sydansk taught the

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[9] *See* Examples 1-3.
[10] *See* Office action dated September 18, 2009 at pages 5-6.
[11] 383 U.S. 1, 17, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966).
[12] *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1739 (2007).
[13] *In re Clay*, 23 U.S.P.Q.2d 1058, 1060 (Fed. Cir. 1992).
[14] *Id.*

> use of a gel in unconfined and irregular volumes within generally underground natural oil-bearing formation to channel flow in a desired direction; Clay teaches the introduction of gel to the confined dead volume of a man-made storage tank.[15]

However, the Federal Circuit disagreed with the Office and held that Clay's field of endeavor was "*storage* of refined liquid hydrocarbons" and Sydansk's invention was directed to the "*extraction* of crude petroleum."

When a reference has the same purpose as the claimed invention, it relates to the same problem, and that fact supports use of that reference in an obviousness rejection; but when a reference has a purpose different from that to which the claimed invention is directed, one skilled in the foreign art might or might not have reason to modify for some alien purpose; but the artisan concerned with the inventor's problem would have no motivation to consider the reference at all, as a candidate for modification or otherwise.[16]

The purpose of the Notenbomer patent is to develop core-shell particles that can bind sodium preferentially over divalent cations.[17] Although Notenbomer states that the core-shell particles can be used to remove potassium from a gastrointestinal tract, binding and removing sodium and potassium from the gastrointestinal tract are very different problems. For example, there are many differences between binding sodium and potassium even though they are similar target ions. These differences include variances in the relative and absolute amounts of sodium and potassium along the gastrointestinal tract; the amounts of sodium and potassium depending upon the condition suffered by the patient; and the selectivity of a cation exchange polymer for sodium and potassium ions.

The amount of sodium as compared to the amount of potassium available for binding will be different because the relative and absolute amounts of sodium and potassium in the gastrointestinal tract change depending on location (e.g., distance from the stomach). Notenbomer recognizes this difference by relying on sodium being present in high amounts in comparison to the relatively low concentration of potassium (p. 3, lines 3-6). Also, Fordtran et al.,[18] studied the sodium and potassium concentrations in the upper GI after different meals, (see especially Figs 2, 4 and 10), found that at the end of the ileum, the sodium concentration is

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[15] *Id.*

[16] *Id.*

[17] *See* U.S. Patent No. 5, 833,854 at column 1, lines 62-64.

[18] J.S. Fordtran et al. "Ionic Constituents and Osmolality of Gastric and Small-Intestinal Fluids after Eating," *Am. J. Digestive Dis.* **1966**, *11(7)*, 503.

relatively high, whereas the potassium concentration is relatively low. However, at the end of the gastrointestinal tract, the contents have a relatively high potassium concentration and a relatively low sodium concentration.[19]

Further, when a subject suffers from hyperkalemia, the body compensates for the high intracellular potassium concentration in various ways, and thus, the amount of sodium or potassium found within the gastrointestinal tract in a hyperkalemic patient can be much different from the sodium and potassium concentrations of healthy people or patients suffering from various diseases. For example, clinical evidence shows that hyperkalemic patients with renal dysfunction or chronic kidney disease (CKD) who are not on dialysis increase potassium excretion in the terminal colon, as described in the review by Musso.[20] Specifically, Musso states:

> During CKD, the small intestine makes a greater contribution to potassium excretion than it does under normal conditions. Intestinal potassium excretion rises during chronic renal failure and the body can eliminate an additional 10–20 mmol of potassium by this route. Colonic potassium secretion begins to adapt when glomerular filtration is reduced to around one-third of normal and when renal failure is advanced, this route may account for as much as 30–70% of total potassium excretion.

This means that depending on the patient's condition, the same cation-binding polymer can have a different effect on potassium and sodium concentrations in the body. Patients on drugs that affect potassium secretion, such as potassium sparing and non-potassium sparing diuretics, will have various perturbations in their sodium/potassium balance that may affect potassium and sodium availability in the gastrointestinal tract. Thus, these patients could also experience a different effect on potassium and sodium concentrations in the body upon administration of a cation-binding polymer.

The reasoning that a skilled person would have been motivated to combine the Notenbomer and Cohen teachings to produce a stable coated cation exchange resin can be compared to that in *Clay*, where the PTO asserted that the claimed invention and the Sydansk reference were of a common endeavor because they were directed to "maximizing withdrawal of

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[19] O. Wrong et al., "*In Vivo* Dialysis of Faeces as a Method of Stool Analysis," *Clin. Sci.* **1965**, *28*, 357-375. (see Figures 2 and 4).

[20] C.G. Musso, "Potassium Metabolism in Patients with Chronic Kidney Disease (CKD), Part I: Patients Not on Dialysis (Stages 3-4)," *International Urology and Nephrology* **2004**, *36*, 465-468.

petroleum stored in petroleum reservoirs."[21] But in this case, the PTO articulates no reason why the Cohen patent is analogous art to either the invention or Notenbomer. Applicants' endeavor is development of oral potassium binders that have increased selectivity by using a coating of the claimed thickness.[22] The Cohen patent is directed to methods of coating particles in order to develop coated islet cells for treating diabetes. The encapsulation of the cells by the coating provides "immunoisolation of the cell by providing a semi-permeable barrier between the host and the transplanted tissue."[23] While the Office states that the reason the Cohen patent and the Notenbomer patent can be combined is because of an "expected result of a stable coated cation exchange resin,"[24] this reason does not place Applicants' invention in the same field as the Cohen patent nor does it address the problem disclosed in Applicants' specification or the still different problem discussed in the Notenbomer patent.

In arguendo, using Notenbomer as the primary reference, the second step of the *Graham* analysis requires consideration of the differences between the prior art and the claims at issue. The Notenbomer patent discloses core-shell particles having a nucleus and a coating wherein the nucleus is a cation exchange material and the coating comprises a membrane that is permeable for monovalent cations. This coating is disclosed as being more permeable for monovalent cations than for bi- or higher valent cations. Exemplified cation exchange materials are polyphosphate and polystyrene sulfonate resins. Exemplified coatings are cellulose acetate and crosslinked polyethyleneimine. Thus, the difference between the instant claims and Notenbomer's core-shell particles is the claimed shell thickness (claim 3) or the claimed shell to core weight ratio (claim 53).

Because the claimed shell thickness or claimed shell to core weight ratio was not disclosed in the Notenbomer patent, the Examiner has recognized that the pending claims are not anticipated by the Notenbomer patent. In formulating a rejection of the claims under § 103(a), the Examiner has found no art that relates to the problem to which the Notenbomer patent relates, but instead has resorted to the Cohen patent as disclosing the coating thickness and shell to core weight ratio required by claims 3 and 53, and forcibly combined the Cohen patent with

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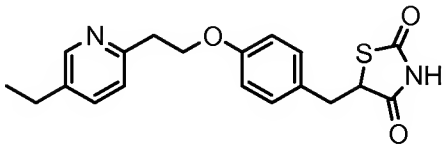
[21] *Id.*
[22] *See* specification at paragraph [0019] and original claim 43.
[23] *See* U.S. Patent No. 6,558,665 at column 8, lines 26-28.
[24] *See* Office action dated September 18, 2009 at page 6.

the Notenbomer patent to support the assertion that pretty much any, but especially the claimed pharmaceutical composition comprising core-shell particles would have been obvious.

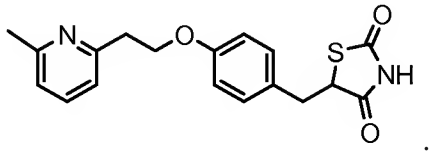
It is well established law, that, where, as here, the patent at issue claims a chemical compound, the analysis of the *Graham f*actor i.e., the differences between the claimed invention and the prior art, turns initially on the structural similarities and differences between the claimed compound and the prior art compounds.[25] Obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound.[26]

In *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*,[27] the Federal Circuit addressed the obviousness issue for structurally similar chemical compounds. In *Takeda*, the claim at issue recited pioglitazone (5-{4-[2-(5-ethyl-2-pyridyl)ethoxy] benzyl}-2,4-thiazolidinedione.") having the following structure:



The ethyl substituent is attached to the 5-position on the pyridyl ring.

Alphapharm filed an ANDA to manufacture and sell a generic version of pioglitazone. According to Alphapharm, Takeda's claimed compound would have been obvious over the prior art compound TZD ("compound b": a pyridyl ring with a methyl (CH_3) group attached to the 6-position of the ring)[28], having the following structure:



Alphapharm argued that one of ordinary skill in the art would select compound b for antidiabetic research and then make "two obvious chemical changes: first, homologation, i.e., replacing the methyl group with an ethyl group, which would have resulted in a 6-ethyl

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[25] *See Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1377; 81 USPQ2d 1324 (Fed. Cir. 2006).

[26] *See Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356; 83 USPQ2d 1169 (Fed. Cir. 2007).

[27] 492 F.3d 1350 (Fed. Cir. 2007).

[28] *Id.* at 1354.

compound; and second, 'ring-walking,' or moving the ethyl substituent to another position on the ring, the 5-position, thereby leading to the discovery of pioglitazone."[29]

The district court found, however, that one of ordinary skill in the art would not have selected compound b from the "hundreds of millions" of possible compounds. "[T]he prior art did not suggest to one of ordinary skill in the art that compound b would be the best candidate as the lead compound for antidiabetic research."[30] The Federal Circuit affirmed and held that there was no motivation to select a particular prior art compound (e.g., compound b) from the universe of prior art compounds and even if there was such a motivation, nothing in the prior art would have led a skilled person to modify compound b to arrive at the claimed compound. Thus, when determining the obviousness of new chemical compounds, there must be "some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness."[31]

Once a reason to modify a known compound is found, the skilled person must also have a reasonable expectation that such a modification will be successful or beneficial in some way. In many chemical cases a "reasonable expectation of success" is not always found, as the Federal Circuit stated in *Eisai Co. v. Dr. Reddy's Laboratories, Inc.*[32] :

> First, KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, KSR presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. See Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007). ("Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."). Third, the Supreme Court's analysis in KSR presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions," 127 S. Ct. at 1742. In Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008), this court further explained that this "easily traversed, small and finite number of alternatives . . . might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a

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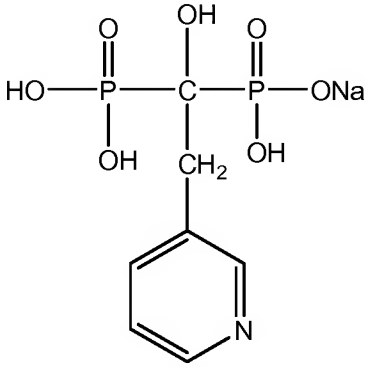
[29] *Id.* at 1357.
[30] *Id.* at 1358.
[31] *Id.*
[32] *Eisai Co. v. Dr. Reddy's Laboratories, Inc.*, 87 U.S.P.Q.2d 1452 (Fed. Cir. 2008).

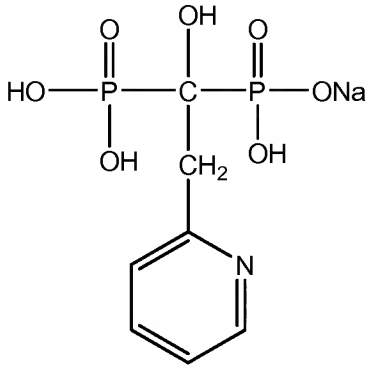
difficult hurdle because potential solutions are less likely to be genuinely predictable. (Emphasis added)

As *KSR v. Teleflex* and *Takeda v. Alphapharm* emphasize, it is important to "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does."[33] There is no reason for the forced combination.

As another instructive example, consider *Procter & Gamble Co. v. Teva Phamaceuticals*,[34] where risedronate, a bisphosphonate which is a bone resorption inhibitor, was the subject of the challenged claims. Risedronate and its closest prior art compound, 2-pyrEHDP are shown below. Risedronate and 2-pyrEHDP are positional isomers.



risedronate



2-pyrEHDP

Although Teva argued that a chemist would have conceived of the positional isomers, the court held that due to the positional change of the nitrogen atom, the isomers differ in three dimensional shape, charge distribution, and hydrogen bonding properties and hence are not obvious over each other. Further, there was evidence that the bisphosphonate art was unpredictable, so there was no reasonable expectation that a modification would have been successful.

Just like Alphapharm in *Takeda*, the PTO is arguing that it would have been obvious to one of ordinary skill in the art to choose the specific polymeric coatings of Cohen from the millions of possible available coatings in the prior art because the coating methods were similar. As *KSR v. Teleflex* and *Takeda v. Alphapharm* emphasize, it is important to "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements

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[33] *KSR v. Teleflex, Inc.*, 82 U.S.P.Q.2d 1385, 1396.

[34] 566 F.3d 989, 90 U.S.P.Q.2d 1947 (Fed. Cir. 2009).

in the way the claimed new invention does."[35] Although the Office states that the similar coating methods and the expected result of a stable coated cation exchange resin would be the reason for combining the references, similar to *Ex parte Meagher*, such a general statement for the reason for combining the references does not address the specific claim elements, e.g., why one would select the Cohen patent from the multitude of references describing the same coating method.[36] The question is not whether there is a reason to make an improvement. That is essentially always the case. The question is whether there is a reason to make a particular modification, and if so, whether there is any expectation of an improvement.

The Office has not provided a reason for the modification of the shell thickness or shell to core weight ratio with enough particularity to establish a *prima facie* case of obviousness. Further, there is no reason provided in the cited art or reliance on knowledge in the art that would have led a skilled person to select the core-shell particles from Notenbomer and the coating thickness or shell to core weight ratio from Cohen to make pharmaceutical compositions comprising core-shell particles as required by claim 3 and 53.

Even if the PTO is relying on the Cohen reference as non-analogous art recited to show the common knowledge of one of ordinary skill in the art, no reason is provided as to why a skilled person would have had reason to select the narrow range of shell thickness in the Cohen patent to modify the core-shell particles of the Notenbomer patent. Indeed, any contrived reason would be contrary to the fact that the Cohen patent cannot properly be combined with the Notenbomer patent because a skilled person would not have considered the teachings of Cohen (directed to encapsulating cells to prevent transplant rejection) when developing core-shell particles that have a shell thickness that increases the amount of potassium bound by the particles. For example, core-shell particles can advantageously have a shell that is thick enough to meaningfully reduce the permeability of the shell polymer for divalent cations. Also, core-shell particles can have shells thin enough to maintain an acceptably high permeability rate for monovalent cations. Cohen describes a coating that is not used to increase the amount of potassium bound by a polymeric core and Cohen provides no suggestion that the coatings would

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[35] *KSR v. Teleflex, Inc.*, 82 U.S.P.Q.2d 1385, 1396.

[36] *Ex parte Meagher*, Appeal no. 2008-3613; Application No. 10/380,898 decided September 22, 2008 at page 15 (describing that combining references for the purpose of "obtaining a conversion coating having good corrosion resistance and good top coat adhesion properties-which are likely goals of virtually every conversion coating composition-do not provide the ordinary coating formulations chemist with a reason to systematically vary" the prior art compositions to arrive at the claimed composition.).

perform to solve the problem facing the claimed invention so that the skilled person would use such a coating to modify the particles of Notenbomer. Thus, the two patents are not in the same field of endeavor and do not address the same problem, so they are not analogous art. Also, Cohen does not evidence common general knowledge of a person of ordinary skill in the art that would have provided a reason to combine the two patents.

Applicants submit that the PTO is engaging in the exact hindsight bias that the Court has repeatedly urged must be avoided. The PTO has not provided a reason why a skilled person would choose the coating thicknesses or shell to core weight ratios as described in the Cohen patent. Hence, the only way that the PTO could arrive at this conclusion is based on the teachings of the instant application while disregarding what the art would have actually led a skilled person to do.

Further, the Office attempts to make up the deficiencies of the rejections asserting that a only low legal bar exists, stating that it "bears a lesser burden of proof in making out a case of prima facie obviousness for product-by-process claims"[37] because they are not claimed in a conventional fashion. However, the Office mischaracterizes claims 3 and 53 as product-by-process claims. There are no process steps required in claims 3 and 53. Thus, the Office's burden of proof for a case of prima facie obviousness is not decreased for these claims.

In sum, the PTO has failed to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does. There is simply no reason that a skilled person would have combined the Notenbomer and Cohen patents to arrive at the claimed invention.

Claim 34

Claim 34 is directed to a method of treating an animal subject suffering from a disease selected from the group consisting of renal insufficiency, renal failure, end stage renal disease (ESRD) and combinations thereof, comprising administering to the subject in need thereof an effective amount of the pharmaceutical composition of claim 3 or 53. Since claim 34 requires administration of a pharmaceutical composition of claim 3 or 53, it is patentable over Notenbomer in view of Cohen for at least the same reasons as claims 3 and 53.

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[37] *See* Office action dated September 18, 2009 at page 5 quoting *In re Fessmann*, 489 F.2d 742, 744, 180 U.S.P.Q. 324, 326 (C.C.P.A. 1974).

Further, for claim 34, the Office simply ignores the requirement that the subject is suffering from renal insufficiency, renal failure, end stage renal disease (ESRD), or a combination thereof as required by claim 34. Therefore, the elements of claim 34 are not disclosed in the cited references, at all. The Office asserts that this limitation is merely a future intended use for the dosage form; but as discussed in detail above, this limitation greatly affects how a patient body chemistry is functioning, and whether the references cited even have a place in the obviousness conversation.[38]

In *Jansen v. Rexall Sundown, Inc.*,[39] a claim directed to a "method of treating or preventing macrocytic-megaloblastic anemia in humans" by "administering a ... vitamin preparation to a human in need thereof...."[40] was construed by the Federal Circuit as follows.

> [T]he claims' recitation of a patient or a human "in need" gives life and meaning to the preambles' statement of purpose. *See Kropa v. Robie*, 187 F.2d 150, 152 [88 U.S.P.Q. 478] (C.C.P.A. 1951) (stating the rule that a preamble is treated as a limitation if it gives "life and meaning" to the claim). The preamble is therefore not merely a statement of effect that may or may not be desired or appreciated. Rather, it is a statement of the intentional purpose for which the method must be performed.[41]

Thus, the preamble's requirement that the core-shell particles be administered to a patient suffering from renal insufficiency, renal failure, end stage renal disease (ESRD), or a combination thereof is an element that must be present in the cited references in order to negate patentability of claim 34.

Since the preamble must be given patentable weight, the issue is whether it would have been obvious from the cited references to treat a patient suffering from renal insufficiency, renal failure, end stage renal disease (ESRD), or a combination thereof with core-shell particles having a shell with the claimed thickness or shell to core weight ratio. There can be no basis for inherency where the claim is directed to a method of treating a condition that ordinarily would not have been present in the patients whose treatment is described in the prior art; and there can be no basis for obviousness where the prior art further fails to recognize the potential effect of the treating agent against the condition specified in the claim. As the C.C.P.A. has stated in

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[38] *See* Office action dated September 18, 2009 at page 5.

[39] 68 U.S.P.Q.2d 1154, 1158 (Fed. Cir. 2003).

[40] *See id.* at 1155.

[41] *See id.* at 1158.

reversing an obviousness rejection of a claim to a method of treating a specified condition with a defined treatment agent based on the inherent effect of treating a different condition with a similar agent:

> [Inherency] is quite immaterial if, as the record establishes here, one of ordinary skill in the art would not appreciate or recognize that inherent result, *in re Shetty*.[42]

The method claims at issue in *Shetty* were directed to methods for appetite control and the cited prior art disclosed compounds and dosages useful for combating microbial infestation. The *Shetty* court stated that the Office had "failed to show a reasonable expectation, or some predictability" that the prior art compound disclosed in the first reference would be an effective appetite suppressant if administered in the dosage disclosed in the second reference and that the Office's hindsight assertion that the dosages would make the weight loss method obvious was insufficient.[43] Similar to *Shetty*, claim 34 recites a method for removing potassium in a patient in need thereof and suffering from renal insufficiency, renal failure, end stage renal disease (ESRD), or a combination thereof by administering core-shell particles having a shell of the claimed thickness or the claimed shell to core weight ratio while Notenbomer discloses methods for treating hypertension by administration of core-shell particles and Cohen is directed to treating diabetes. Thus, claim 34 is patentable over the cited references.

Moreover, the court in *Ex parte Zbornik* found a process for treating Air Sac Infection in fowl patentable over prior art disclosing substantially the same compound to treat ducks for malaria.[44] The *Zbornik* court found that the claims were patentable because the cited reference was not concerned with appellant's problem and it failed to suggest its solution. Similarly, the cited references are concerned with treating hypertension by administration of core-shell particles and treating diabetes with coated islet cells, and they fail to suggest to a skilled person that the claimed core-shell particles would have been beneficial to remove potassium from a patient in need thereof and suffering from renal insufficiency, renal failure, end stage renal disease (ESRD), or a combination thereof.

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[42] 195 U.S.P.Q. 753 (C.C.P.A. 1977).
[43] *See id.* at 756.
[44] *Ex parte Zbornik*, 109 U.S.P.Q. 508 (B.P.A.I 1956).

B. 35 U.S.C. § 103 Rejection over Notenbomer in view of Cohen and Chong

Reconsideration is respectfully requested of the rejection of claims 3, 34, 40, and 53 as unpatentable over Notenbomer (EP 0 730 494) in view of Cohen et al. (U.S. Patent No. 6,558,665) and Chong et al. (U.S. Patent No. 4,389,590) under 35 U.S.C. § 103(a).

Claims 3 and 53

Claims 3 and 53 are described in more detail above. Notenbomer and Cohen are described above. Chong et al. (the '590 patent) describe liquid cation exchange materials comprising emulsions of submicroscopic, spherical beads having diameters from about 0.01 to about 1.5 microns and having from about 0.7 to about 1.5 cation exchange functional groups per monomer unit wherein the cation exchange functional groups are strong acid groups or free acid forms of weak acid groups. The reference further describes that strongly acidic resins in the sodium form can be used for treating hyperkalemia. The Office asserts that from the "suggestion of the '590 patent to use acid cation ion exchange resins to treat hyperkalemia, the artisan of ordinary skill would have been motivated to apply the composition of the '494/'665 patent combination in order to remove excess potassium ions from the body effectively treating hyperkalemia in a human patient in need of treatment."[45]

As described above, claim 3 and 53 require the shell component of the core-shell particle to be a crosslinked polymer having either a specific shell thickness or a specific shell to core ratio. Cohen describes various coating for islet cells for treating diabetes. Further, Chong does not describe any shell materials, is directed to preparing an exceptionally small particle size, spherical ion exchange resins, and is only cited for the disclosure that strongly acidic resins in the sodium form can be used for treating hyperkalemia. In fact, the particle size of Chong et al. is so small (less than 1.5 microns) that such small particles would be absorbed by the body, and thus not function to bind potassium in the gastrointestinal tract (See Payne at al., Nature, 1960 – suggesting that particles in the 1-5 micron range can pass through the small intestine wall and move throughout the body). Thus, Chong is not properly combined with Notenbomer because Chong is not directed to the problem of providing a core-shell particle that can bind potassium in

[45] *See* Office action dated September 18, 2009 at pages 6-7.

the gastrointestinal tract as required by claims 3 and 53 and it is not directed to the problem of Notenbomer.

Further, as described above, the Office has provided no reason why the Cohen patent would have been selected from the universe of coated particles to modify the Notenbomer particles and Chong does not remedy that deficiency. Moreover, although the Office states that it would have been obvious to use the cation exchange polymers to treat hyperkalemia, the Office provides no reason why the polymers of the Chong reference would have been selected from the universe of cation exchange polymers. Further, the combination of the Notenbomer and Chong teachings does not provide a teaching of the shell thickness required by claim 3 or the shell to core weight ratio required by claim 53. If it is asserted that these limitations are inherently met by Notenbomer, such an assertion is improper. The *Spormann* court stated that obviousness and inherency are different questions and "[t]hat which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown."[46] Thus, since it is unknown whether the Notenbomer particles would have the claimed elements, the claimed pharmaceutical compositions cannot be obvious from the Notenbomer disclosure and there is no cogent reasoning why a skilled person would combine the teachings from the cited references to arrive at the claimed invention.

Claims 34 and 40

Claim 34 is described above. Claim 40 is directed to a method of treating an animal subject suffering from hyperkalemia comprising administering the subject in need thereof an effective amount of the pharmaceutical composition of claim 3 or 53. Claims 34 and 40 depend from claims 3 and 53 and are patentable for at least the same reasons as claims 34 and 40. Further, for claims 34 and 40, the Office ignores the requirement that the subject is suffering from renal insufficiency, renal failure, end stage renal disease (ESRD), or a combination thereof or suffering from hyperkalemia. Therefore, the elements of claim 34 and 40 are not disclosed in the cited references.

As described above and in *Jansen v. Rexall Sundown, Inc.*,[47] the preamble's requirement that the core-shell particles be administered to a patient suffering from renal insufficiency, renal

[46] *In re Spormann*, 150 U.S.P.Q. 449, 452 (C.C.P.A. 1966).
[47] 68 U.S.P.Q.2d 1154, 1158 (Fed. Cir. 2003).

failure, end stage renal disease (ESRD), or a combination thereof or suffering from hyperkalemia is an element that must be present in the cited references in order to negate patentability of claims 34 and 40.

Since the preamble must be given patentable weight, the issue is whether it would have been obvious from the cited references to treat a patient suffering from renal insufficiency, renal failure, end stage renal disease (ESRD), or a combination thereof or suffering from hyperkalemia with core-shell particles having a shell with the claimed thickness or shell to core weight ratio. There can be no basis for inherency where the claim is directed to a method of treating a condition that ordinarily would not have been present in the patients whose treatment is described in the prior art; and there can be no basis for obviousness where the prior art further fails to recognize the potential effect of the treating agent against the condition specified in the claim. As described in detail for claims 3 and 53, there is no cogent reasoning why a skilled person would have combined the teachings of Notenbomer, Cohen, and Chong to arrive at the claimed method of treatment. Further, similar to *Shetty*, claims 34 and 40 recites a method for removing potassium in a patient in need thereof and suffering from renal insufficiency or renal failure by administering core-shell particles having a shell of a particular thickness or shell to core weight ratio while Chong discloses that its resins can be used for treating hyperkalemia and Notenbomer discloses methods for treating hypertension by administration of core-shell particles. Thus, claim 34 and 40 are patentable over the cited references.

In sum, claims 3, 34, 40, and 53 are patentable in view of the cited references.

C. 35 U.S.C. § 103 Rejection over Notenbomer in view of Cohen, Shimizu and Macek

Reconsideration is respectfully requested of the rejection of claims 3, 53, 60, 61, 74, and 75 as unpatentable over Notenbomer (EP 0 730 494) in view of Cohen et al. (U.S. Patent No. 6,558,665), Shimizu et al. (U.S. Patent No. 5,824,339) and Macek et al. (U.S. Patent No. 3,499,960) under 35 U.S.C. § 103(a). Claims 3 and 53 are described in detail above, claims 60, 61, 74, and 75 further require a vinylic or an acrylic or methacrylic monomer. The Office asserts that it would have been obvious "to combine the teachings and suggestions in order to arrive at a palatable oral formulation useful in the treatment of a variety of ion related disorders."[48]

[48] *See* Office action dated September 18, 2009 at page 8.

Notenbomer and Cohen are described above. Shimizu et al. disclose drug delivery systems of effervescent compositions of core-shell powders having a fine granular core spray-coated with a liquid mixture containing a water-soluble polymer, a physiologically active substance, and an enteric coating. Further, Shimizu et al. disclose water-soluble polymers of hydroxypropylcelluose (HPC), polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), methylcellulose, carboxymethylcellulose sodium, sodium polyacrylate, polyvinylalcohol, sodium alginate, guar gum, etc.[49] For use as an enteric coating, Shimizu discloses cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose phthalate (HP-55), hydroxymethylcellulose acetate succinate, acrylic copolymers (e.g. Eudragit L30D-55), carboxymethylethylcellulose, and shellac.[50]

Macek et al. disclose polymers used to remove bile acids; the polymers disclosed are polystyrene resins crosslinked with divinyl benzene and functionalized through chloromethylation of the aromatic rings and replacement of the chlorine atom with a tertiary amine such as trimethyl amine to form a trimethyl ammonium group attached to the aromatic rings. Thus, the polymers are amine polymers that can be coated with carboxypolymethylene crosslinked with polyallyl sucrose or an acrylic acid polymer crosslinked with polyallylsucrose.

Similar to Alphapharm in *Takeda*, the PTO is arguing that it would have been obvious to one of ordinary skill in the art to choose the specific polymeric coatings in Shimizu and Macek from millions of possible available coatings "in order to provide sufficient permeability of potassium ions into the cation exchange core"[51] of the Notenbomer particles. As *KSR v. Teleflex* and *Takeda v. Alphapharm* emphasize, it is important to "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does."[52] As described above, the teachings of Cohen are not properly combined to provide core-shell particles having a thickness that is thick enough to decrease the permeability of divalent cations yet thin enough to exchange monovalent cations in a time frame for the core-shell particles to bind potassium low in the colon. The teachings of Shimizu and Macek do not remedy this deficiency. Shimizu is directed to effervescent compositions that do not contain nondisintegrating shell components. Macek is directed to anion exchange cores with

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[49] *See* U.S. Patent No. 5,824,339 at column 4, lines 40-46.
[50] *See* U.S. Patent No. 5,824,339 at column 7, lines 17-21.
[51] *See* Office action dated September 18, 2009 at page 8.
[52] *KSR v. Teleflex, Inc.*, 82 U.S.P.Q.2d 1385, 1396.

negatively charged shells that bind bile acids (negatively charged ions), and would not bind potassium (a positively charged ion). Further, since the most common bile acids have molecular weights of at least 375 g/mol, the permeability of a coating for particles to bind bile acids (e.g., charge and pore size) would have been much different than the charge and pore size needed to provide the required potassium permeability to the shell component of the claimed core-shell particles. Thus, neither Shimizu nor Macek would have provided a reason for a skilled person to modify the particles of Notenbomer to arrive at the claimed core-shell compositions.

Further, although the Office states that the palatable oral formulations would be the reason for combining the references, similar to *Ex parte Meagher*, such a general statement for the reason for combining the references is likely a goal of every reference concerned with coated pharmaceutical particles for oral administration. Further, there is no reason provided in the cited art or reliance on knowledge in the art that would have led a skilled person to select the coatings of Shimizu or Macek to modify the core-shell particles of the Notenbomer patent. For example, Shimizu and Macek are directed to different problems than Notenbomer or the claimed invention. Notenbomer and the claimed invention are directed to core-shell particles for binding sodium or potassium. In contrast, Shimizu is directed to effervescent compositions that provide delayed release of the active agent and disclose shell polymers that are water soluble. Shimizu further describes acrylic acid polymers as enteric coatings that are intended to disintegrate or dissolve at a particular position in the gastrointestinal tract.

Thus, since the problem of Shimizu is different from Notenbomer's, not only is it not properly combined with Notenbomer, but it does not provide a reasonable expectation that the modified particles would have the claimed elements including shell nondisintegration. Further, Macek is directed to bile acid binders that have a core of an amine polymer and a shell that can be an acrylic acid polymer and provides a palatable composition. An amine polymer core binds anions (e.g., bile acids) and would <u>not</u> be a potassium binding cation exchange polymer as required by the instant claims.

Therefore, the PTO has failed to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does. There is simply no reason that a skilled person would have combined Notenbomer and the Shimizu and Macek patents to arrive at the claimed invention. Applicants submit that the PTO is engaging in the very hindsight bias that the Court has repeatedly urged must be avoided. The

PTO has not provided a reason why a skilled person would have chosen the coatings of Shimizu or Macek from the universe of possible coatings. Hence, the only way that the PTO could arrive at this conclusion is based on the teachings of the instant application while disregarding what the art would have actually led a skilled person to do. Thus, claims 3, 53, 60, 61, 74, and 75 are patentable over Notenbomer (EP 0 730 494) in view of Shimizu et al. (U.S. Patent No. 5,824,339) and Macek et al. (U.S. Patent No. 3,499,960) under 35 U.S.C. § 103(a).

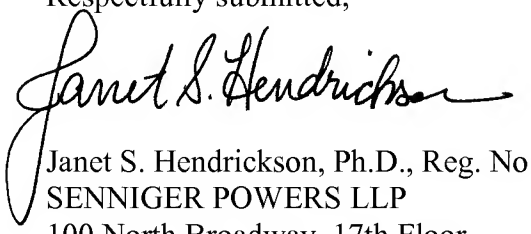
In summary, claims 4, 15, 21, 29, 30, 51, 52, 54-64, and 66-76 depend directly or indirectly from claims 3, 34, 40, and 53 and are patentable over the cited references under 35 U.S.C. § 103(a) for at least the same reasons as discussed above for claims 3, 34, 40, and 53.

VIII. CONCLUSION

For the reasons stated above, Appellants respectfully request that the Office's 35 U.S.C. § 103(a) obviousness rejection of claims 3, 4, 15, 21, 29, 30, 34, 40, 51-64, and 66-76 be reversed.

The Commissioner is hereby authorized to charge any additional fees which may be required to Deposit Account No. 19-1345.

Respectfully submitted,



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IX. CLAIMS APPENDIX

Claims 1-2. (Canceled)

3. An oral or rectal pharmaceutical composition comprising core-shell particles and a pharmaceutically acceptable excipient, said core-shell particles comprising a core component and a shell component, the core component comprising a potassium-binding cation exchange polymer, the shell component comprising a crosslinked polymer having a thickness ranging from about 0.002 microns to about 50 microns, the shell component being essentially not disintegrated during residence and passage through the gastro-intestinal tract of an animal subject.

4. The pharmaceutical composition of claims 3 or 53 wherein said core-shell particles bind potassium ion and retain bound potassium ion during residence and passage through the gastrointestinal tract of a human subject, such that potassium ion is removed from the gastrointestinal tract of the human subject by the core-shell particles to obtain a therapeutic and/or prophylactic benefit.

Claims 5-14. (Canceled)

15. The pharmaceutical composition of claim 3 wherein said core component is physically or chemically attached to said shell component.

Claims 16-20. (Canceled)

21. The pharmaceutical composition of claim 3 wherein said core-shell particle is about 200 nm to about 2 mm in size.

Claims 22-28. (Canceled)

29. The pharmaceutical composition of claim 3 wherein said shell component is deposited with a coating process.

30. The pharmaceutical composition of claim 3 or 53 wherein said pharmaceutical composition further comprises an enteric coating.

Claims 31-33. (Canceled)

34. A method of treating an animal subject suffering from a disease selected from the group consisting of renal insufficiency, renal failure, end stage renal disease (ESRD) and combinations thereof, comprising administering to an animal subject in need thereof an effective amount of the pharmaceutical composition of claim 3 or 53.

Claims 35-39. (Canceled)

40. A method of treating an animal subject suffering from hyperkalemia comprising administering to an animal subject in need thereof an effective amount of the pharmaceutical composition of claim 3 or 53.

Claims 41-50. (Canceled)

51. The pharmaceutical composition of claim 3 or 21 wherein said shell component polymer has a thickness ranging from about 0.005 μm to less than about 10 μm.

52. The pharmaceutical composition of claim 3 or 21 wherein said shell component polymer has a thickness ranging from more than about 1 μm to less than about 10 μm.

53. An oral or rectal pharmaceutical composition comprising core-shell particles and a pharmaceutically acceptable excipient, said core-shell particles comprising a core component and a shell component, the core component comprising a potassium-binding cation exchange polymer, the shell component comprising a crosslinked polymer, the weight ratio of the shell component polymer to the core component polymer ranging from about 0.0001:1 to about 0.5:1, the shell component being essentially not disintegrated during residence and passage through the gastro-intestinal tract of an animal subject.

54. The pharmaceutical composition of claim 53 wherein the weight ratio of the shell component polymer to the core component polymer ranges from about 0.002:1 to about 0.1:1.

55. The pharmaceutical composition of claim 3 or 53 wherein the core component comprises a crosslinked cation-exchange polymer.

56. The pharmaceutical composition of claim 3 or 53 wherein the core component comprises a cation-exchange polymer comprising acidic functional groups.

57. The pharmaceutical composition of claim 3 or 53 wherein the core component comprises a cation-exchange polymer comprising functional groups selected from the group consisting of carboxylate, phosphonate, sulfate, sulfonate, sulfamate and combinations thereof.

58. The pharmaceutical composition of claim 3 or 53 wherein the shell component comprises a crosslinked synthetic polymer.

59. The pharmaceutical composition of claim 3 or 53 wherein the shell component comprises a polymer produced by polymerization of an ethylenic monomer.

60. The pharmaceutical composition of claim 3 or 53 wherein the shell component comprises a polymer produced by polymerization of a vinylic monomer.

61. The pharmaceutical composition of claim 3 or 53 wherein the shell component comprises a polymer produced by polymerization of an acrylic or methacrylic monomer.

62. The pharmaceutical composition of claim 3 or 53 wherein the shell component comprises a hydrophobic polymer, and is essentially not disintegrated during residence and passage of the core-shell particles through the gastro-intestinal tract of a human subject, and wherein the core-shell particles bind potassium ion and retain bound potassium ion during residence and passage through the gastrointestinal tract of the human subject, such that

potassium ion is removed from the gastrointestinal tract of the human subject by the core-shell particles to obtain a therapeutic and/or prophylactic benefit.

63. The pharmaceutical composition of claim 4 wherein the core-shell particles retain at least about 50% of the bound potassium ion with the core-shell particles during residence and passage of the core-shell particles through the gastro-intestinal tract.

64. The pharmaceutical composition of claim 4 wherein the core-shell particles retain at least about 75% of the bound potassium ion with the core-shell particles during residence and passage of the core-shell particles through the gastro-intestinal tract.

65. (Canceled)

66. The pharmaceutical composition of claim 4 wherein the human subject is suffering from renal insufficiency.

67. The pharmaceutical composition of claim 4 wherein the human subject is suffering from renal failure.

68. The pharmaceutical composition of claim 4 wherein the human subject is suffering from end stage renal disease (ESRD).

69. The pharmaceutical composition of claim 4 wherein the human subject is a dialysis patient.

70. The pharmaceutical composition of claim 4 wherein the human subject is suffering from hyperkalemia.

71. The pharmaceutical composition of claim 3 or 53 wherein the shell component is hydrophobic.

72. The pharmaceutical composition of claim 3 or 53 wherein the core component comprises a crosslinked cation-exchange polymer comprising acidic functional groups, and the shell component comprises a crosslinked synthetic polymer.

73. The pharmaceutical composition of claim 72 wherein the shell component is hydrophobic.

74. The pharmaceutical composition of claim 72 wherein the shell component comprises a polymer produced by polymerization of a vinylic monomer.

75. The pharmaceutical composition of claim 72 wherein the shell component comprises a polymer produced by polymerization of an acrylic or methacrylic monomer.

76. The pharmaceutical composition of claim 3 or 53 wherein the oral pharmaceutical composition is in the form of a powder, tablet, capsule, or emulsion.

X. EVIDENCE APPENDIX

None.

XI. RELATED PROCEEDINGS APPENDIX

None.